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Control of Behavior by Drug-Produced Internal Stimuli*

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With 1 Figure in the Text

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Stimuli which are present when a response is reinforced become the occasion for this response on subsequent presentations of these stimuli. When a critical stimulus is altered, a decrement in the response is usually observed. A generalization gradient is produced, and the amount of decrement is a function of the degree of change in the stimulus. That internal stimuli become the occasion for responding has been demonstrated by the classical "drive discrimination" studies (HULL, 1933; LEEPER, 1935) in which animals were trained to make different responses based on "drive" stimuli, inferred from food or water deprivation. The use of chemical agents provides a direct and relatively rapid means of altering internal stimuli and makes possible a more precise evaluation of their role in the formation of stimulus-response-reinforcement relationships.

A response acquired in the presence of a particular set of internal conditions should occur most frequently when these conditions are repeated. Changing these conditions by injection of drugs should result in a response decrement. Likewise, a response acquired under a given drug condition should occur less frequently when this drug is not present. The experiment reported here was designed to investigate these relationships by training rats to respond under particular drug conditions (morphine, dl-amphetamine or placebo) and comparing the number of extinction responses made when these conditions were held constant, with the number made when the drug conditions were changed.

Method

Subjects. Ninety-eight male, Wistar strain albino rats between four and five months old were used as subjects. Eighteen were used to determine the time course of the effects of each of the drugs, while

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eighty were employed in the experiment proper. Following *ad libitum* feeding, animals were reduced to 70% of their weights and, thereafter, weighed daily and fed individually according to their weight gain or loss. In addition, they were deprived of food for 24 hours prior to every trial in the experimental apparatus.

Apparatus. Two Skinner boxes, with modifications described by HILL et al. (1957), were employed. Food (0.1 gram pellets) was dispensed automatically by a rotary disk feeder on a variable interval reinforcement schedule with a 1—$^1/_2$ minute mean. Responses were cumulated on digital counters.

Table 1. *Experimental design*

N	Acquisition	First Extinction	Second Extinction
10	Control	Control	Control
10	Placebo	Placebo	Placebo
10	Amphet-amine	Placebo	Amphet-amine
10	Amphet-amine	Amphet-amine	Amphet-amine
10	Placebo	Amphet-amine	Placebo
10	Morphine	Placebo	Morphine
10	Morphine	Morphine	Morphine
10	Placebo	Morphine	Placebo

Experimental Design. The design which is presented in Table 1 provided for one acquisition session and two extinction sessions, with various combinations of control, placebo, and two drug conditions. Subjects who acquired the lever pressing response under the same drug conditions were divided into two groups for the first extinction session. One group was given the same drug which was administered during acquisition. The other received a placebo during the first extinction session. In addition, for each drug group, a comparison group was provided which received a placebo during acquisition and the drug during extinction. Thus, the following combinations of treatments were given during acquisition and extinction for each of the drugs used: drug-placebo, placebo-drug, and drug-drug. In addition, a control and a placebo group were maintained under constant conditions throughout the experiment.

All animals were given a second extinction session in which the same condition (drug or placebo) as that which obtained during acquisition was reinstated.

Procedure. Preliminary work revealed that the most feasible doses to use were 3 mg/kg of morphine and 2 mg/kg of dl-amphetamine. At higher doses, the animals would not eat readily, while at lower doses, no appreciable effects on lever pressing rate were observed. It was also found that the effects of both drugs were maximal between 60 and 120 minutes after subcutaneous injection. The placebo consisted of 0.15 cc. normal saline, an amount equal to the median volume of the drug injections.

"Magazine" training was limited to placing three pellets in the feeder tray in order to localize activity around the levers. The first five responses were reinforced continuously, i.e. one pellet was given for each response. Thereafter, an aperiodic schedule was employed (variable interval with a 1—$^1/_2$ minute mean). Acquisition sessions lasted one hour.

To avoid development of tolerance and to prevent cumulative drug effects, the first extinction was carried out one week after acquisition. The second extinction was given one week after the first extinction session. Both extinction sessions were one hour long. Except for the absence of reinforcement, all external stimuli such as relay noises were identical with those present during acquisition.

Treatment of Data. During acquisition, responses were cumulated in ten minute segments providing a one hour record of responses in six such periods. Application of Bartlett's test (LINDQUIST, 1953) revealed significant differences in variance. Hence, all data were subjected to square root transformation. Preliminary analysis revealed no significant differences between the control and placebo acquisition groups. Similarly, groups which received the same drug during acquisition were not significantly different. These groups were combined and then submitted to analysis of variance using a "mixed" factorial design. Comparisons between various extinction conditions were made by using the *t*-test.

Results

Acquisition. The effects of dl-amphetamine and morphine on acquisition of the lever-pressing response are shown in Fig. 1, which presents the results in terms of the square roots of the number of responses made within six, 10 minute periods during the 1 hour training session.

The impression that there are distinct differences in the number of responses emitted under both amphetamine and morphine conditions, as compared with the placebo, is confirmed by the analysis of variance applied to these data, the summary of which is presented in Table 2. It will be noted that significant variance, attributable to drug conditions and to successive acquisition periods, as well as their interactions, was found. The F-ratios obtained in each case exceeded the 0.001 level of confidence.

A further analysis of the differences between amphetamine and placebo conditions was made by comparing the mean response rates within each acquisition period by means of the *t*-test. The mean response rate of the amphetamine-treated animals was significantly higher than that of the animals receiving the placebo injection, within all acquisition periods ($P<0.01$). Similar comparisons between the morphine and placebo groups showed no significant differences between these groups within

the first and second periods; however, the means of the morphine group during the remaining periods were significantly lower than those of the placebo ($P<.01$). The differences between means increased with successive training periods[1].

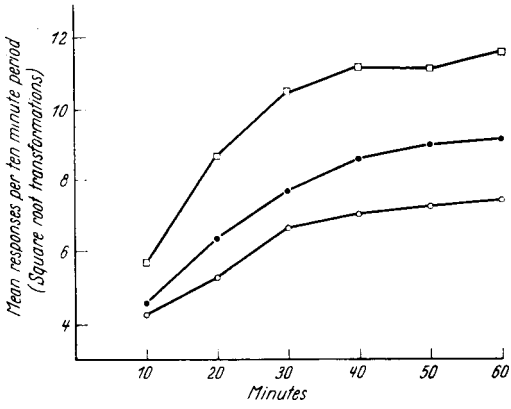

Fig. 1. Effects of dl-amphetamine and morphine on acquisition of the lever-pressing response (transformed data). ●——● Placebo; □——□ dl-amphetamine; ○——○ morphine

Comparisons between the mean response rates before square root transformation showed that the final rate of 139.45 responses per ten minute period, obtained under the amphetamine condition, represents a 162% increase over the placebo rate of 86.13 responses, and a 247% increase over the morphine rate of 56.45 responses during the final period.

Table 2. *Summary of analysis of variance applied to acquisition data of the amphetamine, morphine and placebo groups*

Item	Source	Sums of Squares	*df*	Mean Squares	Items Compared	F-ratio
1	Between Subjects	1239.30	79			
1a	Drugs	759.51	2	379.76	1a/1b	57.02*
1b	Error (b)	479.79	77	6.66		
2	Within Subjects	1699.04	400			
2a	Periods	1275.10	5	255.02	2a/2c	268.44*
2b	Groups X Periods	59.56	10	5.96	2b/2c	6.20*
2c	Error (w)	364.38	385	0.95		
3	Total	2938.34	479			

* <0.001

First Extinction. As will be noted from Table 3, when amphetamine was administered during both acquisition and extinction, the highest extinction mean was obtained. The second highest extinction mean was recorded for the group which received morphine during both acquisition and extinction, while the extinction mean in third highest position

[1] Statistical comparisons which are not crucial to the present discussion are available in the original dissertation.

received the placebo during both acquisition and extinction. Thus, the means for all groups which received the same drug treatments during both acquisition and extinction were higher than the means of groups which received different drug treatments during acquisition and extinction.

The placebo-amphetamine group showed a significantly lower number of extinction responses when compared with the group which received amphetamine during both procedures. The latter mean was also significantly higher than that of the amphetamine-placebo group.

For comparisons involving morphine, the mean extinction score of the group which received morphine during both acquisition and extinction was found to be significantly higher than that of the morphine-placebo group. The morphine-morphine group was also higher than the mean of the placebo-morphine group, but this difference was not statistically significant.

For animals trained under the placebo condition, the group receiving the placebo during extinction as well as during acquisition, was found to be higher than the placebo-morphine and significantly higher than the morphine-placebo group mean.

As stated previously, there were no significant differences in acquisition scores between the various placebo groups which were later subdivided. Thus, any difference in extinction responses under amphetamine or morphine, for groups trained under placebo, would result from specific effects of these drugs on extinction. However, comparisons between the mean responses during extinction under each of these drugs, following conditioning under placebo, revealed that their means were not significantly different (Table 3).

In order to evaluate any difference between the amphetamine and morphine acquisition groups with respect to "retention", a comparison was made between the means for extinction responses when both groups were given the placebo. The result, which is presented in Table 3 shows that the means are not significantly different.

Second Extinction. Table 4 shows the relationships between the means of the various drug conditions during the second extinction session. It should be recalled that, for all groups, the conditions under which the second extinction was carried out were the same as those under which acquisition took place. This provided an opportunity to evaluate the intervening effect of changing drug conditions during the first extinction session.

It will be noted from Table 4 that the highest mean was recorded for the group which received the placebo during acquisition, amphetamine during the first extinction, and placebo during the second extinction. Table 4 shows that the number of responses during the second extinction

Table 3

Comparisons between means obtained on first extinction session (transformed data)

Acquisition Condition	Extinction Condition	Extinction Mean	Mean Diff.	S. E. of Diff.	t	P
Amphetamine	Amphetamine	18.37	8.30	1.362	6.09	< 0.01
	vs.					
Placebo	Amphetamine	10.07				
Amphetamine	Amphetamine	18.37	7.59	0.820	9.27	< 0.01
	vs.					
Amphetamine	Placebo	10.78				
Placebo	Placebo	11.88	1.10	1.011	1.09	> 0.05
	vs.					
Amphetamine	Placebo	10.78				
Placebo	Placebo	11.88	1.81	1.486	1.22	> 0.05
	vs.					
Placebo	Amphetamine	10.07				
Morphine	Morphine	12.76	1.80	1.066	1.69	> 0.05
	vs.					
Placebo	Morphine	10.96				
Morphine	Morphine	12.76	2.97	0.889	3.34	< 0.01
	vs.					
Morphine	Placebo	9.79				
Placebo	Placebo	11.88	2.09	0.891	2.35	< 0.05
	vs.					
Morphine	Placebo	9.79				
Placebo	Placebo	11.88	0.92	1.068	0.86	> 0.05
	vs.					
Placebo	Morphine	10.96				
Amphetamine	Placebo	10.78	0.99	0.926	1.07	> 0.05
	vs.					
Morphine	Placebo	9.79				
Placebo	Morphine	10.96	0.89	1.546	0.58	> 0.05
	vs.					
Placebo	Amphetamine	10.07				

session for this group was significantly higher than the group which received the placebo during all phases of the experiment. The next highest mean recorded was for the group which received amphetamine during acquisition, placebo during the first extinction, and amphetamine during the second extinction session. However, this mean was not significantly different from that of the group which received the placebo throughout the experiment.

For the second extinction session involving morphine and placebo, examination of Table 4 reveals that the largest, and only difference which was significant at the 0.01 level of confidence, was between the group which received morphine during acquisition, placebo during the first extinction and morphine during the second extinction as compared

Table 4

Comparisons between means obtained on second extinction session (transformed data)

Acquisition Condition	First Extinction Condition	Second Extinction		Mean Diff.	t	P
		Condition	Mean			
Amphetamine	Amphetamine	Amphetamine	8.89	2.10	1.33	>0.05
		vs.				
Placebo	Amphetamine	Placebo	10.99			
Amphetamine	Amphetamine	Amphetamine	8.89	1.05	0.49	>0.05
		vs.				
Amphetamine	Placebo	Amphetamine	9.94			
Placebo	Placebo	Placebo	6.38	3.56	1.96	>0.05
		vs.				
Amphetamine	Placebo	Amphetamine	9.94			
Placebo	Placebo	Placebo	6.38	4.61	4.21	<0.01
		vs.				
Placebo	Amphetamine	Placebo	10.99			
Morphine	Morphine	Morphine	8.26	0.20	0.22	>0.05
		vs.				
Placebo	Morphine	Placebo	8.06			
Morphine	Morphine	Morphine	8.26	1.49	1.47	>0.05
		vs.				
Morphine	Placebo	Morphine	9.75			
Placebo	Placebo	Placebo	6.38	3.37	3.29	<0.01
		vs.				
Morphine	Placebo	Morphine	9.75			
Placebo	Placebo	Placebo	6.38	1.68	1.86	>0.05
		vs.				
Placebo	Morphine	Placebo	8.06			

with the group which received the placebo treatment throughout the experiment. As with all comparisons between means on the second extinction session, the higher mean is associated with a return to the drug conditions which existed when the response was acquired, when this followed the first extinction under changed conditions.

Discussion

Comparisons between the amphetamine, placebo, and morphine acquisition curves demonstrated that amphetamine significantly increased mean responses emitted during each of the acquisition periods. Morphine significantly reduced the rate of lever-pressing on all but the first and second ten-minute periods. Animals which acquired the lever-pressing response under the placebo condition produced a smooth, negatively accelerated curve. For animals under the influence of amphetamine, the curve rapidly approached a high maximum rate, but showed little increase during the second half-hour of training. A curve of similar shape was obtained for morphine, except that under the latter condition,

the maximum rate was achieved earlier, and the maximum was much lower than that of the amphetamine or placebo groups.

Although these findings are clearly the result of administration of drugs, they fail to suggest a mechanism through which these changes in behavior are produced. It is clear, however, that amphetamine had a multiplicative effect on response rate during acquisition, while morphine had an opposite action. These effects are quite similar to the transient effects of altering food deprivation. Hence, when such effects are removed, little difference in extinction should be observed. Examination of the mean extinction responses for animals conditioned under amphetamine and extinguished under placebo, as compared with those conditioned under morphine and extinguished under placebo, revealed no significant difference.

The generalization decrement phenomenon suggested that responses acquired in the presence of drug-induced internal stimuli would show greater resistance to extinction when such stimuli were present during extinction, and less resistant when the drug which induced these stimuli was replaced by an inactive (placebo) injection. The converse should also hold. If drug-induced stimuli were not present during acquisition, resistance to extinction would be greater if this state were duplicated in the extinction period.

The extinction data revealed that all relationships were consistent with this prediction, although many of the differences between means did not reach statistical significance. The number of extinction responses was higher when animals were trained and extinguished under the same drug conditions. Animals which acquired the lever-pressing response under either amphetamine or morphine and extinguished under the same drug, made significantly more responses during extinction than animals trained under the drug and extinguished under the placebo condition. The former groups also made a greater number of extinction responses than animals which learned under the placebo condition and were extinguished under either drug.

The results of this experiment are consistent with the generalization decrement phenomenon. Although it might be suggested that specific properties of the drugs employed could account for the obtained results, examination of a number of findings show that this is not the case. Regardless of the drug condition during acquisition or extinction, when this condition was changed, a decrease in extinction responding was observed. The mean of every group which was so changed was lower than that of any group which received the same drug condition during both acquisition and extinction. Having learned under amphetamine or morphine conditions did not result in any difference between mean extinction responses when measured under placebo conditions. Thus,

these findings could not have resulted from any effect of the drug on either acquisition or extinction alone, but must have resulted from the particular operation of *changing* drug conditions between acquisition and extinction.

The results of the second extinction session add additional support to the conclusions based on the findings of the first extinction. A complete analysis of all the factors involved in the second extinction would go beyond the limitations of experimental design. However, the results suggest an interesting secondary effect. The "rebound" or increased responding under these conditions may be due simply to the return to the stimuli present during conditioning, or to the possibility, suggested by HEATHERS and ARAKELIAN (1941), that reduction or absence of responding in extinction is specific to the internal stimuli present when a response is extinguished. Regardless of the mechanism involved, this may have important implications for understanding the effects of behaviorally effective compounds and particularly, for assessing the permanence of effects.

There is increasing experimental evidence that responses acquired under one drug condition and tested under another may result in a response decrement independent of the specific actions of the drug employed. HUNT (1956) found that an emotional response trained under the non-drug state and extinguished under chlorpromazine, reappeared when tested again after the drug effects had dissipated. Similar observations have been made by JACOBSEN and SONNE (1956). Numerous experiments designed to determine the specific behavioral effects of pharmacological agents, including several which were directly concerned with their effects on extinction, have failed to consider the possibility that responses acquired under one drug condition and tested under another may result in a response decrement attributable to internal stimulus changes. Indeed, the typical dose-effect relationship shows a remarkable similarity to the curve which might be expected on the basis of a generalization decrement. Obviously, changes in internal stimuli could not account for many of the reported effects of drugs. However, the results of the present study suggest that this possibility should be considered in the design of psychopharmacological experiments.

A thorough experimental analysis of this effect would require an experimental arrangement whereby direct manipulation of the drug stimulus and correlated changes in response rate are observed. An approach to this has already been made by COOK et al. (1960) who conditioned leg flexion in dogs using epinephrine, norepinephrine, and acetylcholine.

The results of the present investigation suggest that internal responses produced by drug stimuli, such as those which occur consequent

to administration of amphetamine and morphine, may be useful as tools for manipulating internal states. This would appear to be of particular value as an experimental approach to the extensive theorizing about internal responses which are said to mediate behavior. Internal stimuli have been invoked as intervening variables in several major theoretical formulations of behavior. The demonstration that drugs can be employed as tools for precise manipulation of internal stimuli would make possible an objective experimental analysis of theories which appeal to these hypothetical mediation processes. This approach might also provide a method for the analysis of "acquired drives" by specifying more accurately how internal states come to govern responsiveness or sensitivity to external objects or events.

Summary

Groups of rats were trained on a lever-pressing response under morphine, dl-amphetamine and placebo conditions. In order to assess the effects of changing internal stimuli, comparisons were made between groups extinguished under the same drug conditions, with those extinguished under different drug conditions.

A greater number of extinction responses were made by those groups which received the same drug during both procedures. In a second extinction session, all animals received the same drug as that given during acquisition. A greater number of responses were emitted by those groups which were previously exposed to extinction under a drug condition different from that under which the response was acquired. While all comparisons did not reach significance, all were in the direction consistent with the generalization decrement phenomenon. The use of drugs for manipulating internal states is discussed.

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